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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,938	04/05/2006	Yusuke Nakamura	082368-001800US	8069

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/20/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,938	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02-02-06, 10-16-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant response of 10-16-2006 has been entered. With regard to restriction requirements, Applicant election **without traverse** of Group I drawn to claims 1-3 is acknowledged. Applicant election of the following species is acknowledged: CDH3 as listed as number 40 on Table 1, accession number X63629. Claims 4-24 have been cancelled. Claims 1-3 are pending for examination to which the following ground of rejection apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 refers to "high expression levels" and "low expression levels" of a marker gene (e.g., CDH3 or cadherin). Claims 2 and 3 depend on claim 1 are included in this rejection. The terms "low" and "high" are relative terms such that the metes and bounds of the terms cannot be determined in the absence of any established baseline for comparison. As such, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of diagnosing colorectal tumors in a patient having colorectal tumors [AW1], comprising:

a) measuring a level of a Cadherin 3 in a colon cancer cell-containing sample from said colorectal tumor patient, and

b) comparing the level of a Cadherin 3 in said sample to a reference level of Cadherin 3 from normal colon epithelia, wherein a higher level of Cadherin [AW2]3 in said sample as compared to the reference level correlates with diagnosis of colorectal tumors of said patient.

The specification does not provide an enabling disclosure for determining the diagnosis of colorectal tumor by measuring the level of Cadherin 3 alone. The specification teaches that comparison of the level of a gene marker sample from differentiated adenocarcinomas of a patient and their corresponding normal mucosae of the colon to identify genes whose expression is most relevant to distinguish between two diagnosis, such as normal and cancerous colon (p. 21, lines 26-31).

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a method for detecting colorectal cancer by merely comparing levels of a marker gene expression in a specimen and do not indicated how any detected changes in expression reflects on the efficacy of the diagnosis. The specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including expression profiles of gene markers in colon cancer tissues as related to non-cancerous colonic musosae have to be examined and considered for patentability regarding the broadly claimed methods of diagnosing colorectal tumor in a patient.

The instant specification discloses on pages 21 and 22, extraction of total RNA and T-7 based RNA amplification that yield amplified RNA (aRNA) from each of the eleven differentiated adenocarcinomas, nine adenomas and their corresponding normal tissue of the same colon patient sample. The aRNA from each tumor and from normal epithelium were labeled with Cy3-dCTP and Cy5-dCTP respectively and the average ratio Cy3/ Cy5 analyzed to determined a higher level of Cadherin 3 in said sample as compared to level of Cadherin 3 from said reference level sample. [AW3], down-regulation or not change of said marker genes in the

patient sample (p. 22, lines 4-23). While the specification discloses in Table 1 that the level of Cadherin 3 is higher than the expression level in a normal sample and thus the patient is judged to be affected with a colorectal tumor, the specification does not provide any reference level for the expression of Cadherin 3 in any of the normal tissues other than the colon normal epithelial tissue from which this cancer tumors were derived, nor demonstrate that a similar correlation between high expression level of Cadherin 3 and diagnosis of colon carcinoma exists in any other tissues other than colon tumors and correlated normal colon tissue. Thus, the teachings of the specification, while broadly suggesting that Cadherin 3 expression alone can be used as diagnostic of colorectal cancer (e.g., p. 4, lines 13-15, lines 20-23; p. 6, lines 28-29), only provides evidences for determining diagnosis of a colorectal cancer patients by comparing in the same patient expression of gene markers in cancer tumor and corresponding normal colon mucosae.

At the time of filing, a variety of biomarkers for tumors had been identified. However, the skilled artisan was aware that tumors arising form different tissues express different sets of biomarkers. Moreover, analysis of gene-expression at various stages of a particular cancer, e.g., colon cancer will vary. For example, Sinicrope et al., (1999, Clin. Can. Res. Vol. 5, 1793-1804) teaches that the lack of diagnostic value of p53 expression on survival in colon carcinoma is dependent on the stage of the tumor, citing the work of Ahnen et al., who demonstrated that while p53 staining is not diagnosis for stage II colon carcinoma, it does have diagnostic benefits for stage III colon carcinoma (Sinicrompe et al., p. 1801, col. 1). Lin et al., (2002, Oncogene, pages 4120-4128) bring similar insight into the unpredictability of using gene markers as a diagnostic tool when they teach that " the scoring system [molecular diagnosis score] must be

validated using bulk tumors before it can become a tool for clinical diagnosis" (p. 4126, col. 2). Thus, the prior art demonstrates that the diagnostic value of any particular marker depends on the tumor type and the stage of the tumors.

As set forth above by the nature of the invention, the state of the prior art, neither the prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to employ a method for diagnosis of colorectal other than the establishment of high expression of Cadherin 3 as a diagnostic tool for colorectal cancer in relation to expression of the gene marker in corresponding normal colon mucosa of the same patient. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant method to identify an enormous number of methods as broadly or generically claimed, with a resultant identification of a method of diagnosing colorectal tumor in a mammal as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of 35 U.S.C. 102(e) which forms the basis for all obviousness rejections set forth in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Berger et al., US Patent Application Publication 20030148314, Date of Publication Aug. 7, 2003)[AW4]

Berger et al., teach a diagnostic method of assessing whether a patient is afflicted with colon cancer comprising the steps of assessing a) the level of expression of a marker of the invention in a patient sample, and b) the normal level of expression of the marker in a control non-colon cancer sample (p. 2, [0013] [0015]). Additionally, Berger et al., disclose that a significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with colon cancer (p. 2, [0015]). Moreover, Table 1 (p. 4, [0060]) discloses under marker N41, the gene name Cadherin 3, type 1, P-cadherin that is overexpressed in colon cancer cells compared to normal colon cells (i.e., non-cancerous) (p. 4, [0060]). Thus Berger et al., teach the same marker as set forth and claimed in the instant invention. Current claim 1.

Berger et al., teach on Tables 1 a list of markers of the invention along with the sequence listing identifier of the cDNA sequence of a mRNA encoded by each marker gene which is used to quantify level of expression (p. 4, [0060]; p. 10, [0113]). Moreover, Berger et al., teach markers n1-n319 are useful in detecting primary and metastatic colon tumors. (p.4, [0062]). Current claim 2.

Additionally, Berger et al., anticipate that the levels of expression of a plurality of marker genes can be assessed simultaneously using a single substrate (e.g. a "gene chip" microarray of polynucleotides fixed at selected positions)(p.19, [0018]). Current claim 3.

Thus, Berger et al., teach all the claimed limitations and anticipates Applicant's claimed invention.

Conclusion

Claims 1-3 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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